Jarosz Piotr M., Idzik Zuzanna, Gołacki Jakub, Obel Ewa. Thyrotropinoma - the case report about one of the rarest type of pituitary adenomas. Journal of Education, Health and Sport. 2022;12(4):25-33. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.04.002
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.04.002
https://zenodo.org/record/6420088

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 25.03.2022. Revised: 25.03.2022. Accepted: 07.04.2022.

Thyrotropinoma - the case report about one of the rarest type of pituitary adenomas

Piotr M. Jarosz [1], Zuzanna Idzik [1], Jakub Gołacki [1], dr n. med. Ewa Obel [2]

1. Students Scientific Association at Department of Endocrinology, Medical University of Lublin, Chodźki Street 19, 20-093 Lublin, Poland

2. Department of Endocrinology, Medical University of Lublin, Jaczewskiego Street 8, 20-090 Lublin, Poland

Piotr M. Jarosz; pjarosz196@gmail.com; ORCID: 0000-0003-0489-2600;

Zuzanna Idzik; zuzannaidzik@gmail.com; ORCID: 0000-0001-7678-2545;

Jakub Gołacki; kuba.golacki@gmail.com; ORCID: 0000-0001-8502-3030;

Ewa Obel; ewa.obel@umlub.pl; ORCID: 0000-0003-2961-8843;

Abstract

Pituitary tumours are a significant diagnostic problem in clinical practice. Considering all the rarity of thyrotropic hormone secreting adenoma it is a diagnostic and therapeutic challenge in part due to the lack of the preoperative standards. TSH-oma, besides hyperthyroidism symptoms, might be a cause of other endocrine disorders, most often dysfunction of other tropic axes and may cause neurological symptoms associated with sella expansion. We report a case of a 49-year-old male patient with macroadenoma, overt clinical hyperthyroidism, secondary adrenal insufficiency and hypogonadotropic hypogonadism. The diagnosis of thyrotropinoma was confirmed by blood tests that revealed elevated FT3 and FT4 levels together with high TSH. Thyrotropin-releasing hormone (TRH) test was

performed and magnetic resonance imaging (MRI) imaging revealed the presence of macroadenoma. Histopathology examination confirmed the diagnosis of thyrotropic cell pituitary adenoma. The appropriate therapy for thyrotropin pituitary adenoma has not been elaborated in reports of this domain. Preoperatively the patient was prepared by long-acting somatostatin analogue (Sandostatin LAR) injections to reduce tumor size with good therapeutic effect afterwards underwent surgical transsphenoidal treatment successfully. However, specific treatment guidelines for pituitary thyrotropic tumors need to be elaborated more in details.

Key words: thyrotropinoma; secondary hyperthyroidism; somatostatin analogue; case report;

Introduction

A group of pituitary adenomas is widely described in the literature. According to the WHO classification of endocrine organs tumours revised in 2017 (4th edition) seven histological types of pituitary adenoma include: somatotroph, lactotroph, thyrotroph, corticotroph, gonadotroph, null-cell and plurihormonal and double adenomas (1).

Pituitary adenomas are benign proliferation arising from adenohypophyseal cells and comprise approximately 10% to 15% of all intracranial masses (2) . The most frequent type of pituitary adenoma is prolactinoma and it is reported from 32 to 66% cases followed by non-functioning adenomas (15 to 54%) (2,3) Thyrotropin-secreting pituitary adenoma (TSH-oma) is considered the rarest type of pituitary adenomas and it is mentioned in approximately
1% cases with less than 500 cases reported in November 2020 (3,4) . It usually occurs in 40-50 year-old people (2–5). The first case of TSH-oma was described in 1960 (6).

Clinical manifestation in cases with thyrotropin-secreting adenomas reveal goiter (93%), thyroid nodules (70%) and an increased concentration of thyroxine (FT4) and triiodothyronine (FT3) free fractions with uninhibited secretion of thyroid-stimulating hormone (TSH) (7) . Symptoms include signs of hyperthyroidism, namely fatigue and low exercise tolerance, nervousness, increased perspiration, hand tremors, diarrhea, weight loss, heat intolerance and tachycardia, among others. Majority of pituitary secreting adenoma patients are classified as pituitary macroadenomas, due to long-term asymptomatic development of the tumour (8–10) . Superiorly expanding adenoma may compress the optic chiasm and lead to mass effect induced headaches (11) . Additionally, destruction or compression of the pituitary gland may cause complete or partial hypopituitarism (10).

Case report

Diagnosis

In January 2015 a 49 years old man was admitted to the Clinical Department of Endocrinology, Diabetology and Metabolic Disorders, due to clinical signs of hyperthyroidism manifested as: weakness, weight loss, increased perspiration, cardiopalmus, anxiety and chronic headaches. The assessment of endocrine homeostasis was performed. The patient has been reporting these symptoms for 2 years, but he has never been diagnosed endocrinologically. During early ambulatory diagnostics, increased levels of thyroid-stimulating hormone (TSH) - 6,14mIU/L (N: 0,4-4,9), free triiodothyronine (FT3) - 27,3 pmol/L (N:3,0-7,0) and free thyroxine (FT4) - 47,0 pmol/L (N12,0-22,0) were noted. Physical examination revealed a multinodular goiter. While the patient was staying in the hospital in 2013, he said that due to a traffic accident, a head CT scan was performed. According to the patient's medical record “significantly widening architecture in sella turcica area and thinning of bones - pituitary adenoma suspicion” was described.

In the Clinical Department of Endocrinology, Diabetology and Metabolic Disorders, laboratory tests including anti-thyroid gland antibodies level and thyrotropic axis hormone level were performed. Tests examined in our clinic were not significantly different

comparatively to the previous analysis. No anti-thyroid gland antibodies were detected. In February 2015 a head MRI scan was performed (figure 1).

Secondary adrenal gland and gonadal insufficiency was indicated in laboratory tests in April 2015, with pressure of the adenoma on the cerebral infundibulum noted as a probable cause. Blood levels of thyroid-stimulating hormone (TSH), FT4 and FT3 were measured and a thyrotropin-releasing hormone (TRH) test was performed to confirm the diagnosis of secondary hyperthyroidism due to a pituitary macroadenoma.

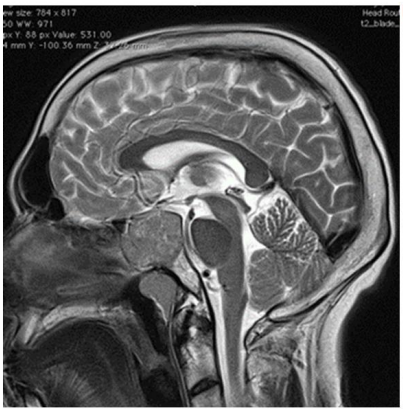

Figure 1 *MRI scan in February 2015*

Imaging findings revealed a tumor-like lesion, probably pituitary macroadenoma, encasing the sella turcica, the clivus as well and invading sphenoidal sinus and suprasellar cisterns. Intense contrast enhancement is detected and enlarged 37 x 33 x 34 mm (CCxLRxAP). Macroadenoma pushes on optic nerves and chiasm. Cerebral infundibulum was covered. It was supposed that tumour mass infiltrated right cavernous sinus.

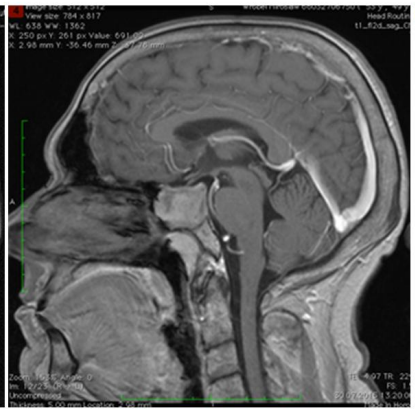

Figure 2 *MRI after 3 injections of Sandostatin LAR*

Adenoma enlarged 25 x 26 x 30 mm (CCxLRxAP) and encased the sella turcica, the clivus as well and invaded sphenoidal sinus and suprasellar cisterns. Cerebral infundibulum is relocated to the right. Optic chiasm intactness. Perhaps, tumour mass infiltrated right cavernous sinus

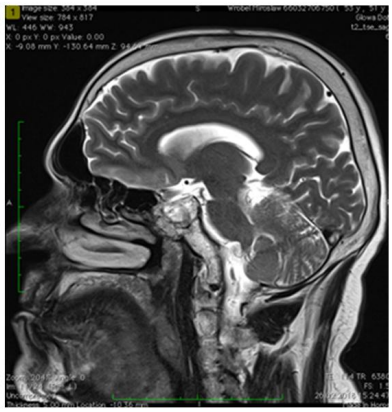

Figure 3 *MRI scan after transsphenoidal resection*

Residual changes in the sella turcica area were presented. Dimensions were not exceeded 2,3 x 1,5 x 2,3 mm (CCxLRxAP). Cerebral infundibulum is relocated to the right. Optic chiasm intactness.

Treatment

From January to July 2015 the patient was treated with thiamazole (methimazole) until normalisation of thyroid hormones. Besides that, he was prepared for the surgical transsphenoidal treatment through preoperative long acting octreotide injections in four 30 mg doses. Substitution therapy of hydrocortisone in 30 mg/day dose was implemented due to secondary adrenal insufficiency.

In July 2015, before surgical treatment, after 4 long-acting somatostatin analogue (Sandostatin LAR) injections, a control MRI scan was made (figure 2). During radiological evaluation a tumour-like lesion was noted.

In August 2015 transsphenoidal resection of adenoma was performed. In histopathological examination, the immunohistochemical profile demonstrated a positive expression of TSH hormone receptor: TSH(+), GH(+/-), PRL(-), LH (-), FSH(-). In electron microscopy slides thyrotropin features were noted.

After the operation oral L-thyroxine and hydrocortisone treatment, as well as testosteron prolongatum injections were implemented. In 2016 control MRI scans were performed *(fig. 3)*.

Discussion

Pituitary adenoma secreting TSH hormone is a rare cause of hyperthyroidism that can be also called central hyperthyroidism. TSH-omas are infrequent, they comprise even less than one percent of pituitary adenomas (3,10) . Majority of this type of adenomas are secreting TSH only, but ca. 30% TSH-omas are associated with hypersecretion of other pituitary hormones (mixed TSH-omas), most often growth hormone (GH), prolactin (PRL) or gonadotropins (10). TSH-oma occurs with equal frequency in men and women, it can appear at any age but average age at diagnosis is 45 years (2,3,5).

The diagnosis of TSH-oma is usually delayed until the stage of invasive macroadenoma. In the moment of diagnosis our patient's adenoma was of considerable size which was causing symptoms not only relevant to hormonal activity, but also mass effect. For the first time, a tumour was incidentally detected in a head CT scan performed because of a traffic accident that took place in October 2013. Even though the CT scan suggested the presence of a pituitary lesion, the diagnostic process was not conducted. Almost two years later our patient reported symptoms such as weakness which led off to start the diagnostic process.

It seems that the diagnostic criteria of the European Thyroid Association are helpful especially when the diagnosis is unclear (13). Evidence-based science suggests that MRI may be helpful in ruling out TSH-secreting pituitary adenomas and its sensitivity is estimated to circa 98% (11,12).

Physical examination of patients with thyrotropinoma usually shows goiter and clinical symptoms of hyperthyroidism of varying severity. In most cases, during examination, the pituitary tumour reaches the size of a macroadenoma and neurological symptoms like headache and visual disturbance might be even more evident than hyperthyroidism symptoms itself (7) . Symptoms that were visible in our patient are weakness, weight loss, increased perspiration, heart racing, anxiety, diastema and chronic headaches. Nodular goiter was found. Thyroid function tests revealed high FT3 and FT4 levels with high TSH. Thyroid autoantibodies were not detected. Besides symptoms associated with hormonal function of adenoma there might also be conditions arising from hormonal insufficiency in other glands caused by mass effect on healthy pituitary cells. Insufficiency of the anterior pituitary gland

in our patient’s case was revealed as secondary hypoadrenocorticism and hypogonadism, both requiring substitution treatment.

Laboratory tests show elevated levels of thyroid hormones (FT3 and FT4) with high or normal TSH. As a diagnosis confirmation thyrotropin-releasing hormone (TRH) test seems to be the most specific, due to allowing the distinction between TSH-secreting pituitary tumours and the pituitary variant of resistance to thyroid hormone (PRTH) syndrome (4,13,14). Normally, stimulation with TRH results in increased secretion of TSH, but in TSH-omas there is unresponsive (4,14). In our case TRH test confirmed the primary diagnosis of secondary hyperthyroidism. A test with short-acting somatostatin showed about 40% decreased TSH level suggesting the presence of somatostatin receptors on tumour cells (4,13).

Clinical manifestation of secondary hyperthyroidism may be milder than hormone blood levels would suggest. It is necessary to differentiate this condition with primary hyperthyroidism originating from thyroid disease that is very common and avoid

inappropriate treatment like thyroidectomy or radioiodine therapy. Early diagnosis of pituitary adenoma and proper treatment might prevent endocrinological and neurological complications attributable to tumour growth.

There are three treatment aims for pituitary adenomas. Tumour size decrease, hormonal correction and preparing for surgical treatment are mentioned as general objectives during therapy (2,5,6,8,12). Unfortunately, the appropriate therapy for thyrotropin pituitary adenoma has not been elaborated in reports of this domain. Evidence based medicine describes somatostatin analogues or dopamine agonists as one of therapy options of TSH-secreting adenomas (8). The best initial treatment is transsphenoidal surgical resection of macroadenoma (12,13). Variety of current studies demonstrate that presurgical pharmacotherapy with octreotide acetate or long-term acting somatostatin analogue may decrease thyrotropin secretion. This kind of treatment has also been shown to shrink the tumour mass, similarly to the effects in the treatment of acromegaly. Thus, these medications can be useful and decrease remission probability after operation (12,13,15–17).

In this case, radiologic evaluation showed regressive character of tumour-like lesion due to pharmacological treatment. Macroadenoma reduced its mass in every dimension from 37 x 33 x 34 mm (CCxLRxAP) in the first MRI scan to 25 x 26 x 30 mm (CCxLRxAP) directly before transsphenoidal resection. Significant shrinkage of the tumour mass was reported in even ca. 50% patients receiving somatostatin analogue (12). The mechanism of action has not been yet established.

Table 1 shows decreased level of TSH during Sandostatin LAR treatment. These indicate that even just one injection of somatostatin analogue normalised thyrotropin level. In our case, treatment with octreotide resulted in inhibition of TSH level and reduction of clinical symptoms of hyperthyreosis after the first dose. Literature reported TSH suppression of serum TSH within 7 days after Sandostatin injection. In medical reports, normalization of TSH levels has been found in 88–92% of the patients treated with octreotide (12,18).

Table 1. TSH level during Sandostatin LAR treatment;

date	24-04-15 (thiamazole treatment only)	13-05-15 (before 1st Sandostatin LAR injection)	10-06-15 (before 2nd Sandostatin LAR injection)	10-07-15 before 3rd Sandostatin LAR injection)	07-08-15 (before 4th Sandostatin LAR injection)	02-09-15 (after TSA and IV Sandostatin LAR injection)	17-10-15 control examination
TSH [mIU/L]	12,408	6,567	1,863	1,668	1,489	0,854	<0,008

Transsphenoidal tumour resection is recommended as the treatment of choice (12) . Joonho Byun et al. reported that in 13 of 14 cases of surgical treatment of TSH - oma showed excellent surgical outcomes (19) . In our case, surgical treatment was performed after 4 injections of octreotide analogue with successful TSH normalisation. What's more, there is a known case of tumour size decrease after octreotide LAR therapy prominent enough to omit surgical treatment (20).

Conclusions:

Our case shows potential therapeutic effect of Sandostatin LAR in TSH-secreting pituitary adenoma. Octreotide-LAR appears to be a great therapeutic tool and it may be useful as a complement to surgical treatment in order to obtain more favorable anatomical conditions. Nevertheless, transsphenoidal tumour resection seems to be the best method of treatment. However, specific treatment guidelines for pituitary thyrotropic tumors need to be elaborated in detail.

References

1. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta neuropathologica [Internet]. 2017 Oct 1 [cited 2021 Nov 4];134(4):521–35. Available from: https://pubmed.ncbi.nlm.nih.gov/28821944/
2. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. JAMA [Internet]. 2017 Feb 7 [cited 2021 Nov 4];317(5):516–24. Available from: https://pubmed.ncbi.nlm.nih.gov/28170483/
3. The Epidemiology of Pituitary Adenomas - ClinicalKey [Internet]. [cited 2021 Nov 4]. Available from: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0889852920300256?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0889852920300256%3Fshowall%3Dtrue&referrer=https:%2F%2Fpubmed.ncbi.nlm.nih.gov%2F
4. Luo P, Zhang L, Yang L, An Z, Tan H. Progress in the Pathogenesis, Diagnosis, and Treatment of TSH-Secreting Pituitary Neuroendocrine Tumor. Frontiers in Endocrinology. 2020 Nov 27;11.
5. Diagnosis and treatment of pituitary adenomas - PubMed [Internet]. [cited 2021 Nov 4]. Available from: https://pubmed.ncbi.nlm.nih.gov/15765032/
6. Thyrotropin-secreting pituitary adenomas: biological and molecular features, diagnosis and therapy - PubMed [Internet]. [cited 2021 Nov 4]. Available from: https://pubmed.ncbi.nlm.nih.gov/18923369/
7. Azzalin A, Appin CL, Schniederjan MJ, Constantin T, Ritchie JC, Veledar E, et al. Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. Pituitary [Internet]. 2016 Apr 1 [cited 2021 Nov 4];19(2):183–93. Available from: https://pubmed.ncbi.nlm.nih.gov/26689573/

8. Losa M, Fortunato M, Molteni L, Pereiti E, Mortini P. Thyrotropin-secreting pituitary adenomas: Biological and molecular features, diagnosis and therapy. Minerva Endocrinologica [Internet]. 2008 Dec [cited 2021 Nov 4];33(4):329–40. Available from: https://neuro.unboundmedicine.com/medline/citation/18923369/Thyrotropin_secreting_pituitary_adenomas:_biological_and_molecular_features_diagnosis_and_therapy_
9. Arafah BM, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. The Journal of clinical endocrinology and metabolism [Internet]. 2000 May 1 [cited 2021 Nov 4];85(5):1789–93. Available from: https://pubmed.ncbi.nlm.nih.gov/10843153/
10. Lake MG, Krook LS, Cruz S v. Pituitary Adenomas: An Overview. American Family Physician [Internet]. 2013 Sep 1 [cited 2021 Nov 4];88(5):319–27. Available from: www.aafp.org/afp
11. Beck-Peccoz P, Persani L, Lania A. Thyrotropin-Secreting Pituitary Adenomas. Endotext [Internet]. 2019 Jan 11 [cited 2021 Nov 4]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK278978/
12. Beck-Peccoz P, Persani L, Lania A. Thyrotropin-Secreting Pituitary Adenomas. Endotext [Internet]. 2019 Jan 11 [cited 2021 Nov 4]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK278978/
13. Aron DC, Tyrrell JB, Wilson CB. Pituitary tumors. Current concepts in diagnosis and management. Western Journal of Medicine [Internet]. 1995 [cited 2021 Nov 5];162(4):340. Available from: /pmc/articles/PMC1022773/?report=abstract
14. FAGLIA G. The Clinical Impact of the Thyrotropin-Releasing Hormone Test. Thyroid. 1998 Oct;8(10):903–8.
15. Erem C, Hacihasanoglu A, Sari A, Ersöz HÖ, Ukinç K, Fidan S. A rare case and a rapid tumor response to therapy. Endocrine 2004 25:2 [Internet]. 2004 [cited 2021 Nov 5];25(2):141–5. Available from: https://link.springer.com/article/10.1385/ENDO:25:2:141
16. Kienitz T, Quinkler M, Strasburger CJ, Ventz M. Long-term management in five cases of TSH-secreting pituitary adenomas: a single center study and review of the literature. European Journal of Endocrinology [Internet]. 2007 Jul 1 [cited 2021 Nov 5];157(1):39–46. Available from: https://eje.bioscientifica.com/view/journals/eje/157/1/1570039.xml
17. van Varsseveld NC, Bisschop PHLT, Biermasz NR, Pereira AM, Fliers E, Drent ML. A long-term follow-up study of eighteen patients with thyrotrophin-secreting pituitary adenomas. Clinical endocrinology [Internet]. 2014 Mar [cited 2021 Nov 5];80(3):395–402. Available from: https://pubmed.ncbi.nlm.nih.gov/23848527/
18. Socin HV, Chanson P, Delemer B, Tabarin A, Rohmer V, Mockel J, et al. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. European Journal of Endocrinology [Internet]. 2003 Apr 1 [cited 2021 Nov 5];148(4):433–42. Available from: https://eje.bioscientifica.com/view/journals/eje/148/4/433.xml
19. Byun J, Kim JH, Kim YH, Cho YH, Hong SH, Kim CJ. Thyroid-Stimulating Hormone-Secreting Pituitary Adenomas : Single Institutional Experience of 14 Consecutive Cases. Journal of Korean Neurosurgical Society [Internet]. 2020 [cited 2021 Nov 5];63(4):495–503. Available from: http://www.jkns.or.kr/journal/view.php?doi=10.3340/jkns.2019.0169

20. Erem C, Hacihasanoglu A, Sari A, Ersöz HÖ, Ukinç K, Fidan S. A Rare Case and a Rapid Tumor Response to Therapy: Dramatic Reduction in Tumor Size During Octreotide Treatment in a Patient with TSH-Secreting Pituitary Macroadenoma. Endocrine [Internet]. [cited 2021 Nov 5];25(2):141–6. Available from: https://www.academia.edu/23336047/A_Rare_Case_and_a_Rapid_Tumor_Response_to_Therapy_Dramatic_Reduction_in_Tumor_Size_During_Octreotide_Treatment_in_a_Patient_with_TSH_Secreting_Pituitary_Macroadenoma